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Health and Environmental Effects Profile for Dichlorobutenes

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR DICHLOROBUTENES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
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16. ABSTRACT

The Health and Environmental Effects Profile for Dichlorobutenes was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for Dichlorobutenes.

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

TABLE OF CONTENTS

		page
	EXECUTIVE SUMMARY	vi
1.	INTRODUCTION	-1-
2.	ENVIRONMENTAL FATE AND TRANSPORT PROCESSES	-3-
3.	EXPOSURE	-6-
4.	PHARMACOKINETICS	-7-
5.	EFFECTS	-8-
6.	AQUATIC TOXICITY	-18-
7.	EXISTING GUIDELINES AND STANDARDS	-19-
8.	APPROACHES TO RISK ASSESSMENT	-20-
9.	REFERENCES	-22-

EXECUTIVE SUMMARY

Some experimental and calculated data are available pertaining to the environmental fate and transport of or human exposure to 1,4-dichloro-2-butene and 3,4-dichloro-1-butene. Based on calculated data both of these compounds are expected to persist in the aquatic media.

Limited information is available on the biological effects of 1,4-dichloro-2-butene. Acute studies indicate that this compound is highly toxic to rats following oral and inhalation exposure, and severe skin and eye damage was caused in rabbits by topical application of the undiluted compound. Brief summaries of 2- and 4-week short term inhalation studies with rats indicated that exposures in the range of 8-12 ppm caused respiratory tract inflammation.

Subcutaneous or intraperitoneal injection of 1,4-dichloro-2-butene into mice produced low incidences of local sarcomas. When tested by skin application and in two-stage carcinogenesis experiments (1,4-dichloro-2-butene was used as an initiator), however, significant tumorigenic responses were not elicited. It was also briefly noted that inhalation of 1,4-dichloro-2-butene at a level of 5 ppm (duration not stated) produced a significant increase in malignant nasal tumors in rats; available information about this test is so sparse that it cannot be evaluated fully. Provisionally the chemical could be classed as having limited evidence of carcinogenicity according to IARC criteria. The carcinogenic potential of 1,4-dichloro-2-butene is further supported by positive mutagenicity findings (Ames assays, dominant lethal assay with Drosophila), and the potential for metabolism to a reactive epoxide structure.

1,4-Dichloro-2-butene produced wavy ribs in rats in a teratogenicity study. Data regarding the reproductive effects or human effects of 1,4-dichloro-2-butene are not available. The only information found for 3,4-dichloro-1-butene were two incompletely reported positive mutagenicity assays.

1. INTRODUCTION

The scope of this document is limited to the following two dichlorobutenes: 1,4-dichloro-2-butene and 3,4-dichloro-1-butene.

1,4-Dichloro-2-butene (1,4-dichlorobutene, 2-butylene dichloride) is a colorless liquid with a distinct odor (Hawley, 1977), and is commercially produced by the chlorination of butadiene. The 1,4-dichlorobutene available in the United States contains 95-98% trans-1,4-dichlorobutene and 2-5% of the cis isomer (IARC, 1977). Several physical parameters follow:

CAS registry number	764-41-0
Formula	$C_4H_6Cl_2$: $Cl\text{-}CH_2\text{-}CH{=}CH\text{-}CH_2Cl$
Molecular weight	125
Melting point	3.5°C (Hawley, 1977)
Boiling point	158°C (Hawley, 1977)
Specific gravity (25/4°C)	1.186 (Hawley, 1977)
Solubility in water (calculated)	6.3×10^4 mg/ℓ (Mabey et al., 1982)
Log octanol/water partition coefficient (calculated)	1.73 (Mabey et al., 1982) 2.11 (Könemann, 1981)

1,4-Dichloro-2-butene is produced in the United States by Denka Chemical Corp., Houston, Texas; DuPont Co., Victoria, Texas; and Trinity Chemical Corp., San Antonio, Texas (SRI, 1981). In the United States, virtually all of this compound is used as an intermediate in the manufacture of hexamethylenediamine and chloroprene (IARC, 1977).

3,4-Dichloro-1-butene, in addition to cis-1,4-dichlorobutene and trans-1,4-dichlorobutene, is produced by the chlorination of butadiene. Since 3,4-dichlorobutene has a lower boiling point, it can be separated from the other two isomers by distillation (IARC, 1977). Several physical parameters follow:

CAS registry number	760-23-6
Formula	$ClCH_2$-CHCl-CH=CH_2
Molecular weight	125.0
Melting point	115-117°C (Weast, 1980)
Density (g/mℓ) at 20°C	1.1170 (Weast, 1980)
Solubility in water	3.2×10^4 mg/ℓ (Mabey et al., 1982)
Log octanol/water partition coefficient (calculated)	2.01 (Mabey et al., 1982)

3,4-Dichloro-1-butene is produced in the United States by Denka Chemical Corp., Houston, Texas (SRI, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Pertinent data regarding the environmental fate and transport processes of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene were not located in the available literature. However, some theoretical predictions about the aquatic fate and transport of these two chemicals can be made. The sediment sorption partition coefficients for 1,4-dichloro-2-butene and 3,4-dichloro-1-butene from aquatic media can be calculated to fall within the ranges of 0.27-1.66 and 0.43-1.48, respectively, based on the correlation equations of Schwarzenbach and Westall (1981), Briggs (1981) and Kenaga and Goring (1980). The calculated sorption partition coefficients are based on sediments containing 0.5% organic carbon and the values of log octanol/water partition coefficient given in Section 1. Therefore, the estimated log K_{oc}

$$K_{oc} = \frac{\text{Sorption partition coefficient} \times 100}{\% \text{ organic carbon}}$$

values for 1,4-dichloro-2-butene and 3,4-dichloro-1-butene would be in the ranges of 1.74-2.52 and 1.93-2.47, respectively. These log K_{oc} values are close to the experimental log K_{oc} value of 1.92 for benzene (Schwarzenbach and Westall, 1981). Therefore, the transport of these two compounds from aquatic phase to sediment is expected to follow a pattern similar to that of benzene.

Neither of these compounds is expected to undergo photolysis in aquatic media (Mabey et al., 1982).* From the estimated rate constants values of 4×10^{-4} $hour^{-1}$ and 4×10^{-5} $hour^{-1}$ (Mabey et al., 1982), the hydrolysis half-lives for 1,4-dichloro-2-butene and 3,4-dichloro-1-butene in neutral

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*Mabey et al. (1982) caution that their estimated rate constants and calculated physical parameters were intended only for determining the relative contributions of potential degradation or dissipation mechanisms and should not be used to determine absolute rates without further consultation with the authors.

aquatic media can be calculated to be ~72 and 720 days, respectively. The rate constant for the oxidation of 1,4-dichloro-2-butene in aquatic media by peroxy radicals and singlet oxygen has been estimated to be 3 $M^{-1}sec^{-1}$ and 10^4 M^{-1} sec^{-1}, respectively (Mabey et al., 1982). Assuming the concentration of peroxy radicals and singlet oxygen in aquatic media to be 10^{-9} M and 10^{-12} M, respectively (Mill and Mabey, 1980), the half-lives for these two reactions can be calculated to be 7.3 and 2.2 years, respectively. Thus, the oxidation of 1,4-dichloro-2-butene in aquatic media by both peroxy radicals and singlet oxygen is not expected to be a significant fate process. 3,4-Dichloro-1-butene is estimated to be inert regarding aquatic oxidation by both peroxy radicals and singlet oxygen (Mabey et al., 1982).

No experimental information was found regarding the microbial degradability of either of these compounds in the aquatic environment or in soils. Assuming the microbial degradation rate constant of 10^{-10} mℓ $cell^{-1}$ $hour^{-1}$ (Mabey et al., 1982) and the concentration of microorganisms in aquatic media as $5x10^5$ cells $mℓ^{-1}$ (Burns et al., 1981), the biodegradation half-lives of both of these compounds in aquatic media can be calculated to be ~580 days.

Mabey et al. (1982) quite recently have calculated the vapor pressure anticipated at 25°C for both compounds based on their boiling points and enthalpy of vaporization. For 1,4-dichloro-2-butene, the cis isomer vapor pressure is 4.76 mm Hg at 25°C while that for the trans isomer is 4.17 mm Hg. For 3,4-dichloro-1-butene it is 17.3 mm Hg at 25°C. The fate and transport of dichlorobutenes in soil can be partially predicted from their estimated log K_{oc} values. Based on these values the leaching of dichlorobutenes from soil is expected to follow a pattern similar to that of

benzene. No prediction regarding microbial degradability and chemical oxidation in soils can be made at the present time.

It should be emphasized that the fate of a chemical predicted from theoretical calculations, in certain instances, may vary considerably from the experimental data. In the preceding discussions, the fates of the two compounds have been predicted from theoretical calculations because no experimental data were available. However, extreme caution should be exercised in interpreting the predicted fate based on theoretical calculations or estimations. Experimental data is virtually always preferred and should be substituted in prediction schemes at the earliest opportunity.

3. EXPOSURE

Although unspecified isomer(s) of dichlorobutene were detected in the Mississippi River, Louisiana (U.S. EPA, 1976), no quantitative data on the concentration of either of the chemicals in air, water, soil or any other medium are available.

4. PHARMACOKINETICS

4.1. ABSORPTION AND DISTRIBUTION

Pertinent data regarding absorption and distribution of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene were not found in the available literature.

4.2. METABOLISM

Specific information on the metabolism of 1,4-dichloro-2-butene or 3,4-dichloro-1-butene were not found in the available literature. Van Duuren et al. (1975) have noted, however, that 1,4-dichloro-2-butene can conceivably be metabolized to an epoxide which is structurally analogous to open-chain β-chloroethers.

4.3. EXCRETION

Pertinent data regarding excretion of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene were not found in the available literature.

5. EFFECTS

1,4-Dichloro-2-butene available in the United States contains 95-98% trans-1,4-dichloro-2-butene and 2-5% of the cis isomer (Hawley, 1977). Most of the reports of biological effects of 1,4-dichloro-2-butene do not specify the purity of the mixture tested.

5.1. CARCINOGENICITY

trans-1,4-Dichloro-2-butene (purified) has been tested for carcinogenicity in female ICR/Ha Swiss mice by lifetime skin application, and subcutaneous and intraperitoneal injection (Van Duuren et al., 1975). 1,4-Dichloro-2-butene was additionally tested by these investigators in the same strain of mice in a two-stage skin carcinogenesis experiment with phorbol myristal acetate (PMA) as a promoting agent. The design and results of these experiments are summarized in Tables 5-1 and 5-2. As indicated, 1,4-dichloro-2-butene did not elicit local papilloma or squamous carcinoma development in either the skin application or two-stage carcinogenesis studies. When injected subcutaneously or intraperitoneally once per week over lifetime, however, statistically significant ($P<0.05$) low incidences of local sarcomas were produced. It should be noted that the weekly (0.05 mg) dose used to elicit these local tumors was quite low, equivalent to ~1.67 mg/kg, but this was reportedly the highest possible dose that gave minimal cytotoxic effects (Van Duuren et al., 1975). The incidence of tumors distant from the sites of application of 1,4-dichloro-2-butene in the above-mentioned experiments was reportedly comparable to that in the vehicle and no-treatment control groups (i.e., no tumorigenic response was observed except at the site of injection).

Clary (1977) noted that exposure to a nominal airborne 1,4-dichloro-2-butene concentration of 5 ppm produced a statistically significant increase

TABLE 5-1

Tumorigenic Activity of trans-1,4-Dichloro-2-butene
in Female ICR/Ha Swiss Mice Following Subcutaneous, Intraperitoneal, or Dermal Exposure[a]

Route	Compound	Dosage	Vehicle	Application	Days on Test	Median Survival (Time days)	No. of Mice with Local Tumors/ Total No. of Mice on Test			Significance Value (p, Total No. of Local Malignant Tumors)
							Sarcomas	Papillomas	Squamous Carcinoma	
Subcutaneous	1,4-Dichloro-2-butene	0.05 mg	tricaprylin (0.05 mL)	once weekly	537	477	3/30	NT	NT	<0.05
	Bis(chloromethyl)ether	0.3 mg	Nujol (0.05 mL)	once weekly	371[b]	260	21/50[c]	NT	NT	<0.01
	Tricaprylin	0.05 mL	NA	once weekly	570	436	0/50	NT	NT	NT
	Nujol	0.05 mL	NA	once weekly	458	443	1/50	NT	NT	>0.10
	No treatment	NA	NA	NA	570	484	0/85	NT	NT	NT
Intraperitoneal	1,4-Dichloro-2-butene	0.05 mg	tricaprylin (0.05 mL)	once weekly	537	478	2/30	NT	NT	>0.10
	Bis(chloromethyl)ether	0.02 mg	Nujol (0.05 mL)	once weekly	424	287	4/30	NT	NT	<0.05
	Tricaprylin	0.05 mL	NA	once weekly	567	513	0/30	NT	NT	NT
	Nujol	0.05 mL	NA	once weekly	456	441	0/30	NT	NT	NT
	No treatment	NA	NA	NA	570	484	0/85	NT	NT	NT
Skin[d]	1,4-Dichloro-2-butene	1 mg	acetone (0.1 mL)	thrice weekly	537	>537	NT	0/30	0/30	NT
	Acetone	0.1 mL	NA	thrice weekly	537	487	NT	1/30	0/30	NT
	No treatment	NA	NA	NA	570	484	NT	0/85	0/85	NT

[a]Source: Van Duuren et al., 1975

[b]Positive control group was terminated before the others due to poor survival.

[c]One additional animal had a papilloma at the injection site.

[d]Shaved interscapular region

NA = Not applicable; NT = not tested

TABLE 5-2

Two-Stage Carcinogenesis in Female ICR/Ha Swiss Mice with trans-1,4-Dichloro-2-butene as an Initiating Agent and PMA as a Promoter[a]

Primary Treatment[b]	Secondary Treatment[c]	Duration of Test (Days)	Median Survival Time (days)	Days to 1st Papilloma	No. of Mice with Local Tumors/ Total No. of Mice on Test		Significance Value (p, Total No. of Local Malignant Tumors)
					Papilloma[d]	Squamous Carcinoma	
1,4-Dichloro-2-butene	PMA	537	478	83	1/30 (1)	0/30	NA
None	PMA	537	460	358	3/30 (3)	1/30	>0.10
1,4-Dichloro-2-butene	Acetone (0.1 mL)	537	526	NA	0/30	0/30	NA
DMBA	PMA	537	398	58	28/30 (20%)	17/30	<0.01
DMBA	Acetone (0.1 mL)	537	469	NA	0/30	0/30	NA
None	None	537	510	NA	0/60	0/60	NA

[a]Source: Van Duuren et al., 1975

[b]Single application: 1,4-dichloro-2-butene, 1 mg in 0.1 mL acetone; DMBA, 20 µg in 0.1 mL acetone

[c]Thrice weekly beginning 14 days after primary treatment: PMA, 2.5 µg/0.1 mL acetone

[d]Total number of papillomas in parentheses

PMA = phorbol myristyl acetate; DMBA = 7,12-dimethylbenz(a)anthracene; NA = not applicable

in malignant nasal tumors in rats. Rats exposed to 0.5 ppm reportedly showed no adverse effects. A detailed report of this study, which was conducted at the duPont de Nemours and Company, Inc., Haskell Laboratory, has not been published, although attempts are being made at this time to secure it. Since nasal tumors in rats are rare, the animal evidence for the carcinogenicity of trans-1,4-dichloro-2-butene is provisionally judged to be limited according to IARC criteria.

5.2. MUTAGENICITY

The mutagenic effects of 1,4-dichloro-2-butene and 3,4-dichloro-1-butene are summarized in Table 5-3.

Bartsch and co-workers have reported that 1,4-dichloro-2-butene and 3,4-dichloro-1-butene were mutagenic to Salmonella typhimurium strain TA100 in, respectively, Ames plate incorporation and vapor exposure assays (Bartsch et al., 1976, 1980; Barbin et al., 1978). The mutagenic effect was enhanced by the addition of mouse liver homogenate S-9 fraction. The assays with 1,4-dichloro-2-butene were also conducted with human liver microsomal fractions; the activity was comparable to that with mouse liver (Bartsch, 1976). Mukai and Hawryluk (1973) briefly reported in an abstract that 1,4-dichloro-2-butene was mutagenic to S. typhimurium and E. coli, but additional details regarding these studies were not published.

An increased frequency of recessive lethal mutations was produced in Drosophila melanogaster after males were fed 1,4-dichloro-2-butene (77% trans isomer) (Vogel, 1979). These results, shown in Table 5-4, indicate that 1,4-dichlorobutene-2 is an effective mutagen in Drosophila. The cytotoxic activities of this compound made a reduction in exposure time essential in some of the experiments, this being the reason for the variations in the length of exposure. When males were treated with 10.0 mM

TABLE 5-3

Mutagenicity of 1,4-Dichloro-2-butene and 3,4-Dichlero-1-butene

Compound	Type of Assay	Species/Strain	Metabolic Activation	Dose	Application	Response	Reference
1,4-Dichloro-[a] 2-butene	reverse mutation	S. typhimurium/ TA100	yes[b] and no	1.35 µmol/ plate	plate incorporation	+	Bartsch et al., 1976,[c] 1980; Barbin et al., 1978[c]
1,4-Dichloro-2-butene	NS	S. typhimurium/NS	NS	NS	NS	+	Mukai and Hawryluk, 1973[c]
1,4-Dichloro-2-butene	NS	E. coli/NS	NS	NS	NS	+	Mukai and Hawryluk, 1973[c]
3,4-Dichloro-1-butene	reverse mutation	S. typhimurium/ TA100	yes[d] and no	2.6 µmol/ plate[e]	vapor pressure[f]	+	Bartsch et al., 1976[c], 1980; Barbin et al., 1978[c]
3,4-Dichloro-1-butene	sister chromatid exchange, in vitro	Human lymphocytes	NS	NS	NS	+	Gu, 1981[c]

[a]77% trans isomer

[b]S-9 fractions from mouse (PB-induced) and human livers enhanced mutagenicity ~3-fold

[c]Results reported in abstract form

[d]PB-induced mouse liver homogenate S-9 fraction

[e]Quantity of 3,4-dichloro-1-butene determined in aqueous phase of media after vapor exposure in desiccators

[f]Linear dose response curve demonstrated

NS = Not specified

TABLE 5-4

Frequency of Recessive-Lethal (R.L.) Mutations After Treatment of D. melanogaster (Males) with 1,4-Dichloro-2-butene

Treatment	Brood 1			Brood 2			Brood 3		
	Chromosomes Observed	R.L. Mutations	Percent	Chromosomes Observed	R.L. Mutations	Percent	Chromosomes Observed	R.L. Mutations	Percent
2.0 mM x 42 hour	294	1	0.34	201	0	0	199	1	0.50
4.0 mM x 24 hour	330	1	0.30	417	5	1.3	412	7	1.7
2.5 mM x 48 hour	412	8	1.9	405	3	0.74	411	4	0.97
5.0 mM x 24 hour	622	4	0.64	619	2	0.32	620	6	0.97
	1658	14	0.84	1642	10	0.61	1642	18	1.10

1,4-dichloro-2-butene, all the males died within 24 hours, whereas with 5.0 mM the survival rate was ~75%.

Gu (1981) noted that 3,4-dichloro-1-butene markedly increased the frequency of sister chromatid exchanges in human lymphocytes in vitro.

5.3. TERATOGENICITY

Kennedy et al. (1982) tested 1,4-dichloro-2-butene for teratogenicity in ChR-CD rats. Groups of 21-23 pregnant rats were exposed to 0, 0.5 or 5.0 ppm 1,4-dichloro-2-butene for 6 hours/day on days 6 through 15 of gestation. The dams were monitored for body weight gain and overt signs of toxicity; the uterine contents were examined at day 21 of gestation. The rate of weight gain of the dams exposed to 5.0 ppm was significantly reduced ($P<0.05$) relative to that of controls. No other signs of maternal toxicity were observed among treated groups. The numbers of implantations, resorptions, live fetuses/litter and fetal measurements such as fetal weights and crown-rump length were unaffected by treatment. Likewise, the types and incidences of external, visceral and skeletal anomalies and malformations did not differ among litters from control and treated dams, with the exception of a dose-related increase in the incidence of wavy ribs. This abnormality, considered to be a minor anomalie by the authors, occurred in 0 of 23 control litters, 2 of 21 low-dose litters and 7 of 21 high-dose litters.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding the reproductive effects of 1,4-dichloro-2-butene or 3,4-dichloro-1-butene were not located in the available literature.

5.5. CHRONIC OR SUBCHRONIC TOXICITY

Pertinent data regarding the effects of chronic or subchronic exposure to 1,4-dichloro-2-butene were not located in the available literature.

Brief summaries of two unpublished low level, short term, inhalation exposure studies that were conducted at DuPont's Haskell Laboratory were presented by Clary (1977). In the first study, rats and hamsters were exposed to 1,4-dichloro-2-butene at levels of 0.1 or 10 ppm for 2 weeks (schedule not stated). Growth retardation and inflammation of the respiratory tract were observed in the rats that were exposed to 10 ppm, but no effects were seen at 0.1 ppm. No effects were seen in hamsters following exposure at either level. In the second study, rats were exposed to 1,4-dichloro-2-butene for 4 weeks (5 days/week, 6 hours/day) at 0.5, 2, 8 and 12 ppm. Effects that were reportedly similar to those observed after the 2-week exposures were found at 12 and 8 ppm; 2.0 and 0.5 ppm were stated to be no-effect levels. The major effects of the 4-week 12 and 8 ppm exposures were apparently in the respiratory tract. Additional details regarding the design and results of the 2- and 4-week subchronic studies were not provided.

Clary (1977) also noted that 1,4-dichloro-2-butene was being studied at the Haskell Laboratory in both 90-day and lifetime inhalation studies with rats; the studies were being conducted at levels of 0.5 and 5 ppm for 6 hours/day, 5 days/week. The results of these experiments have apparently not been published, but exposure to 5 ppm may be tumorigenic (Section 5.1.).

5.6. ACUTE TOXICITY

The acute lethal and irritant effects of 1,4-dichloro-2-butene are summarized in Table 5-5. As indicated, this compound is highly toxic to rats following single oral and 4-hour inhalation exposures. The dermal toxicity of 1,4-dichloro-2-butene to rabbits is moderately low (LD_{50}=734 mg/kg), but application of undiluted compound to the skin and eyes caused severe irritation and corneal necrosis, respectively.

TABLE 5-5

Acute Lethal and Irritant Effects of 1,4-Dichloro-2-butene

Route	Species/Strain	Sex	Number	Vehicle	Dosage	Response	Reference
Oral (gavage)	rat/NS	NS	5/group	NS[a]	89 mg/kg[b] (41-196)	Range-finding LD_{50} (14-day)	Smyth et al., 1951
Inhalation	rat/NS	NS	6/group	NA	62 ppm[c,d] x 4 hours	2 of 6 died within 14 days	Smyth et al., 1951
Inhalation	rat/NS	NS	6/group	NA	saturated vapor x 8 minutes[e]	Maximum time for 6 rats to survive 14 days	Smyth et al., 1951
Inhalation	rat/NS	NS	NS	NA	86 ppm x 4 hours (77-96)	LC_{50}	Kwon and Waritz, 1960
Intravenous	mouse/NS	NS	NS	NS[a]	56 mg/kg	LD_{50}	NIOSH, 1982
Dermal	rabbit/NS	NS	4/group	NS[a]	734 mg/kg (556-958), single dose occluded 24 hours contact	Range-finding LD_{50} (14-day)	Smyth et al., 1951
Dermal	rabbit/NS	NS	5	undiluted	0.01 mℓ (11.8 mg), uncovered application	Strong erythema, edema or slight necrosis after 24 hours (Grade 5)	Smyth et al., 1951
Ocular	rabbit/NS	NS	5 eyes	undiluted	0.005 mℓ (5.9 mg), corneal application	Severe injury (necrosis) after 18-24 hours (Grade 5)	Smyth et al., 1951

[a]Not specifically stated if the chemical was administered undiluted

[b]Groups of 5 rats administered logarithmic series of doses that differed by a factor of 2

[c]Nominal concentration

[d]Groups of 6 rats exposed to logarithmic series of concentrations that differed by a factor of 2

[e]Groups of 6 rats exposed for logarithmic series of time intervals that differed by a factor of 2

NS = Not specified; NA = not applicable

Single exposures to 1,4-dichloro-2-butene (route, concentration and species not specified) were reported in a Russian study to cause necrotic changes in the central nervous system, kidney, liver, myocardium, stomach, adrenal and testis (Petrosyan et al., 1981); histochemical changes that included reduced RNA (brain, liver, kidney), decreased glycogen (liver) and increased lipids (hepatocytes, hepatic epithelium) were also reportedly observed.

5.7. OTHER RELEVANT INFORMATION

Specific information was not found on the toxicity of 3,4-dichloro-1-butene, but it was noted in a Russian study of chlorobutene structure-activity relationships that this compound is less toxic than 1,4-dichloro-2-butene or 1,3-dichloro-2-butene (Gizhlaryan, 1981). The greater toxicity of 1,4-dichloro-2-butene was attributed to the terminal position chlorine atoms.

6. AQUATIC TOXICITY

Limited information was found on the aquatic toxicity of trans-1,4-dichloro-2-butene. A 7-day LC_{50} value of 39.5 mg/ℓ has been reported for the guppy, Poecilia reticulata. A calculated bioconcentration factor (BCF) of 23.6 indicates that this compound has a low potential for bioaccumulation.

6.1. ACUTE

A 7-day LC_{50} value of >39.5 mg/ℓ was determined for trans-1,4-dichloro-2-butene in a static renewal assay with the guppy, Poecilia reticulata (Könemann, 1981).

6.2. CHRONIC AND PLANT EFFECTS

Pertinent data regarding chronic toxicity and plant effects of 1,4-dichloro-2-butene or 3,4-dichloro-1-butene were not located in the available literature.

6.4. RESIDUE

Specific information regarding residues of 1,4-dichloro-2-butene or 3,4-dichloro-1-butene in aquatic organisms was not found in the available literature. Veith et al. (1980) have suggested, however, the use of the following equation to calculate BCFs:

$$\log BCF = 0.76 \log K_{ow} - 0.23,$$

where K_{ow} is the partition coefficient between octanol and water. Using this equation and the calculated values of $\log K_{ow}$ reported by Könemann (1981) and Mabey et al. (1982), which range from 1.73-2.11, the BCF for whole fish was calculated to be in the range of 12.2-23.6.

6.5. OTHER RELEVANT INFORMATION

Other relevant data regarding 1,4-dichloro-2-butene and 3,4-dichloro-1-butene were not located in the available literature.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

Pertinent data regarding recommended or promulgated ambient or occupational exposure standards or guidelines to protect human health for 1,4-dichloro-2-butene or 3,4-dichloro-1-butene were not located in the available literature.

7.2. AQUATIC

Pertinent data regarding recommended or promulgated ambient exposure standards or guidelines to protect aquatic life for 1,4-dichloro-2-butene or 3,4-dichloro-1-butene were not located in the available literature.

8. APPROACHES TO RISK ASSESSMENT

The available data suggest that 1,4-dichloro-2-butene may be carcinogenic, but are insufficient for derivation of a cancer-based risk assessment.

When injected intraperitoneally or subcutaneously into female ICR/Ha Swiss mice, low incidences of local sarcomas were produced (Van Duuren, 1980). Although only weak sarcomagenic activity was demonstrated, it should be noted that only a single dose level was tested (0.05 mg/mouse), and that this dose was quite low (~1.67 mg/kg). The production of injection-site sarcomas in rodents is not considered to be acceptable evidence that a chemical will be carcinogenic to humans by other routes of exposure (U.S. EPA, 1980). When tested for activity in skin application (1 mg twice weekly for ~19 months) and two-stage carcinogenesis (1,4-dichloro-2-butene was used as an initiator) experiments in the same species of mouse, significant tumorigenic responses were not elicited.

It was briefly noted by Clary (1977) that inhalation exposure to 5 ppm 1,4-dichloro-2-butene (schedule and duration not stated) produced a statistically significant increase in malignant nasal tumors in rats, and that 0.5 ppm did not elicit a response. Clary (1977) also mentioned that intermittent exposure to 1,4-dichloro-2-butene for 2 or 4 weeks caused respiratory tract inflammation in rats at levels of 8-12 ppm, but not at 0.1, 0.5 or 2 ppm. The apparent effect and no-effect levels defined by these short term exposures would appear to be consistent with those observed for nasal tumor induction, but the lack of published detail regarding these Haskell Laboratory studies renders the results inappropriate for use in quantitative risk assessment.

The potential for 1,4-dichloro-2-butene carcinogenicity is also supported by positive (although often incompletely reported) mutagenicity

assays with bacteria and Drosophila (see Tables 5-3 and 5-4), and the potential for metabolism to a reactive epoxide structure (Van Duuren et al., 1975). 3,4-Dichloro-1-butene has been reported to elicit positive mutagenic responses in Ames assays with S. typhimurium and in SCE assays in vitro with human lymphocytes (see Table 5-3), but the latter study was reported only as an abstract.

In a teratogenicity study conducted at Haskell Laboratories (Kennedy et al., 1982), there was a dose-related increase in the incidence of wavy ribs among litters of pregnant rats exposed to 0.5 and 5 ppm 1,4-dichloro-2-butenes. This abnormality was considered to be of minor biological significance by the authors of the study.

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